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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/825,423	04/03/2001	Patricia C. Weber	ID01152	2057

24265 7590 01/10/2007
SCHERING-PLOUGH CORPORATION
PATENT DEPARTMENT (K-6-1, 1990)
2000 GALLOPING HILL ROAD
KENILWORTH, NJ 07033-0530

EXAMINER	
STEADMAN, DAVID J	
ART UNIT	PAPER NUMBER
1656	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/825,423	WEBER ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,7-9,11,21 and 22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *9,11,21 and 22* is/are allowed.

6)☒ Claim(s) *1-3* is/are rejected.

7)☒ Claim(s) *7 and 8* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Appendix A*.

DETAILED ACTION

Application Status

1. Claims 1-3, 7-9, 11, and 21-22 are pending in the application.

2. Applicant's amendment to the claims after final rejection, filed on 28 November 2006, is acknowledged and has been entered. This listing of the claims replaces all prior versions and listings of the claims.

3. Applicant's arguments filed on 28 November 2006 have been fully considered and are deemed to be persuasive to overcome all of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

4. The text of those sections of Title 35, U.S. Code not included in the instant action can be found in a prior Office action.

5. The indicated allowability of claims 1-3 is withdrawn in view of the new rejections that follow. The finality of the Office action mailed on 3 October 2006 is withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claim(s) 1-2 are rejected under 35 U.S.C. 103(a) as being unpatentable over Borowski et al. (*Eur. J. Biochem.* 266:715-723, 1999) in view of Cho et al. (*J. Biol. Chem.* 273:15045-15052; cited as reference AG in the IDS filed on 14 December 2005) and Kim et al. (US Patent 6,183,121).

The claims are drawn to (in relevant part) a polypeptide "defined by" the amino acid sequence set forth in SEQ ID NO:17. The term "defined by" in the claims is interpreted as "consisting of." If applicant intends for the term "defined by" to have a meaning other than "consisting of," applicant is requested to so state and clarify the record.

The reference of Borowski et al. teaches the NTPase and helicase activities of HCV are located at the C-terminal 450 amino acids of NS3 beginning at amino acid 181 (p. 715, left column, bottom). The reference teaches the isolation of a minimal functional domain of Hepatitis C virus (HCV) NTPase/helicase with ATP-binding activity, wherein amino acids 1203-1364 of HCV polyprotein is determined to be such a minimal functional domain (p. 715, abstract). In view of the discussion by Borowski et al. at p. 718, left column, amino acids 1203-1364 of HCV polyprotein correspond to amino acids 176-338 of HCV NS3. The reference teaches that isolation of the minimal functional ATP binding domain of NS3 "may provide a rational basis for the development of effective inhibitors of the NTPase/helicase" (p. 716, left column, top). Borowski et al. does not teach an HCV NS3 helicase fragment of amino acids 181-324.

Cho et al. teaches a crystal structure of RNA helicase of HCV genotype 1b, showing the NTPase domain (p. 15047, left column, Figure 1). According to Cho et al.,

sequence alignment of RNA helicases reveals three highly conserved motifs in the NTPase domain of Figure 1, including amino acids 322-324 of HCV NS3 (p. 15045, right column, bottom), that Thr322 of the conserved motif of amino acids 322-324 of HCV NS3 forms a hydrogen bond with catalytic His293 (p. 15048, Figure 3), and that two of these domains, including amino acids 322-324 of HCV NS3 interact (p. 15048, Figure 3).

The reference of Kim et al. teaches a consensus sequence of HCV NS3 as SEQ ID NO:2, wherein residues 181-324 of SEQ ID NO:2 of Kim et al. are 100% identical to SEQ ID NO:17 herein (see Appendix A).

At the time of the invention, it would have been obvious to one of ordinary skill in the art to combine the teachings of Borowski et al., Cho et al., and Kim et al. to produce the polypeptide of amino acids 181-324 of HCV NS3 as taught by Kim et al. One would have been motivated to produce the minimal fragment of the NTPase domain of HCV NS3 in order to "provide a rational basis for the development of effective inhibitors of the NTPase/helicase" as taught by Borowski et al. One would have been motivated to select amino acid 181 of HCV NS3 as the N-terminal amino acid because this is the first amino acid of the helicase domain of HCV NS3 as taught by Borowski et al. One would have been motivated to select amino acid 324 as the C-terminal amino acid of the fragment because according to Cho et al., residues 322-324 represent a conserved motif and are present in all HCV NS3 helicases and are shown to interact with active site residues of the HCV NS3 helicase ATPase domain. One would have a reasonable expectation of success to produce the polypeptide of amino acids 181-324 of HCV NS3

because of the cloning techniques as taught by Kim et al. Therefore, claims 1-2, drawn to SEQ ID NO:17, would have been obvious to one of ordinary skill in the art.

7. Claim(s) 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Borowski et al. (*Eur. J. Biochem.* 266:715-723, 1999) in view of Cho et al. (*J. Biol. Chem.* 273:15045-15052; cited as reference AG in the IDS filed on 14 December 2005) and Kim et al. (US Patent 6,183,121) as applied to claims 1-2 above and further in view of Ford et al. (*Prot Exp Purif* 2:95-107, 1991) and Xiao et al. (*Cell* 99:545-555, 1999).

Claim 3 is drawn to a polypeptide consisting of SEQ ID NO:3. It is noted that SEQ ID NO:3 is SEQ ID NO:17 with an N-terminal addition of the sequence GSHM.

The references of Borowski et al., Cho et al., and Kim et al. disclose the teachings as describe above. While the combination teaches SEQ ID NO:17, the combination does not teach SEQ ID NO:3.

Ford et al. teaches fusion tails, *e.g.,* an N-terminal histidine tail, can be used to facilitate recovery of a recombinantly produced heterologous protein (p. 95, abstract and p. 100). Ford et al. teaches a protease cleavage site can be incorporated between the tail and the protein of interest and the tail can be removed by cleavage of the fusion protein using the corresponding protease (p. 102).

Xiao et al. teaches the use of vector pET15b for recombinant expression of a heterologous protein in a bacterial cell, wherein the protein expressed using this vector has an N-terminal histidine tag that is cleaved using thrombin, leaving a GSHM sequence at the N-terminus (p. 553, left column).

At the time of the invention, it would have been obvious to one of ordinary skill in the art to combine the teachings of Borowski et al., Cho et al., Kim et al., Ford et al., and Xiao et al. to produce the polypeptide of amino acids 181-324 of HCV NS3 as taught by Kim et al. with an GSHM sequence at the N-terminus. One would have been motivated to produce the polypeptide of amino acids 181-324 of HCV NS3 using the vector of pET15b as taught by Xiao et al. in order to facilitate purification of the polypeptide by virtue of its having an N-terminal histidine tag. One would have been motivated to cleave the fusion protein with thrombin, thus leaving a GSHM sequence at the N-terminus in order to remove the histidine tag as taught by Xiao et al. One would have a reasonable expectation of success to produce the polypeptide of amino acids 181-324 of HCV NS3 as taught by Kim et al. with a GSHM sequence at the N-terminus because of the teachings of Kim et al. and Xiao et al. Therefore, claim 3, drawn to SEQ ID NO:3, would have been obvious to one of ordinary skill in the art.

Conclusion

8. Status of the claims:

Claims 1-3, 7-9, 11, and 21-22 are pending.

Claims 9, 11, and 21-22 appear to be in a condition for allowance.

Claims 1-3 are rejected.

Claims 7-8 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David J. Steadman, Ph.D.
Primary Examiner
Art Unit 1656

APPENDIX A

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US-09-128-314-2
; Sequence 2, Application US/09128314
; Patent No. 6183121
; GENERAL INFORMATION:
;  APPLICANT: Kim, Jospeh L
;  APPLICANT: Morgenstern, Kurt A
;  APPLICANT: Caron, Paul R
;  APPLICANT: Lin, Chao
;  APPLICANT: Vertex Pharmaceuticals Inc.
;  TITLE OF INVENTION: CRYSTAL STRUCTURE OF THE HCV NS3 HELICASE DOMAIN
;  FILE REFERENCE: Sequence listing for VPI/97-101
; Patent No. 6183121
;  CURRENT APPLICATION NUMBER: US/09/128,314
;  CURRENT FILING DATE: 1998-08-03
;  EARLIER APPLICATION NUMBER: 60/055,772
;  EARLIER FILING DATE: 1997-08-13
;  NUMBER OF SEQ ID NOS: 4
;  SOFTWARE: PatentIn Ver. 2.0
; SEQ ID NO 2
;   LENGTH: 631
;   TYPE: PRT
;   ORGANISM: Hepatitis C virus
US-09-128-314-2

  Query Match          100.0%;  Score 743;  DB 2;  Length 631;
  Best Local Similarity  100.0%;  Pred. No. 8.9e-76;
  Matches  144;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps
0;

Qy          1 SPVFTDNSSPPAVPQSFQVAHLHAPTGSGKSTKVPAAYAAQGYKVLVLNPSVAATLGFGA 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        181 SPVFTDNSSPPAVPQSFQVAHLHAPTGSGKSTKVPAAYAAQGYKVLVLNPSVAATLGFGA 240

Qy         61 YMSKAHGVDPNIRTGVRTITTGSPITYSTYGKFLADGGCSGGAYDIIICDECHSTDATSI 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        241 YMSKAHGVDPNIRTGVRTITTGSPITYSTYGKFLADGGCSGGAYDIIICDECHSTDATSI 300

Qy        121 LGIGTVLDQAETAGARLVVLATAT 144
              ||||||||||||||||||||||||
Db        301 LGIGTVLDQAETAGARLVVLATAT 324
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